

**REMARKS**

As a preliminary matter, it should be noted that the Office Action dated July 10, 2006 appears to be missing language at the bottom of page 3. As a result, this response only addresses those issues actually included in the Office Action.

With entry of this Response claims 37-40, 54 and 59-82 are pending in the application. Claims 1-36, 41-53, and 55-58 were previously cancelled without prejudice to their elective further prosecution in any related application(s). No new matter has been added to the application. Consideration of the following remarks is respectfully requested.

**Patentability Under 35 USC §§§ 102 and 103**

Applicants note for the record that the instant application has been examined through numerous rounds of official review by the Office, and that this intensive course of prosecution has left essentially only one remaining issue with respect to patentability to be resolved, namely whether the application satisfies the utility requirement under 35 USC § 101 (as addressed herein below), and in so doing teaches persons skilled in the art how to use the invention (see, discussion of rejection under 35 USC § 112, asserted on identical grounds as utility rejection, below) . On this basis, Applicants understand the record in this application to reflect that the Office has fully considered the merits of the application with regard to all other requirements set forth under 35 USC §§§ 102, 103, and 112, and with respect to other applicable laws and regulations relating to patentability and enforceability within the Office's purview, and has favorably determined that the instant application satisfies all such requirements.

**Patentability Under 35 USC § 101**

As noted above, the only remaining issue in this application is whether claims 37-40, 54 and 59-82 are founded by a credible, specific, or well-established utility sufficient to satisfy the requirements of 35 USC § 101. The Office presently rejects the subject claims on this basis, on the alleged grounds set forth in the Office Action.

Applicants respectfully traverse the asserted grounds for rejection presented in the current Office Action, and submit that the instant disclosure conveys clear utility for the claimed invention that would have been widely recognized and accepted by persons of ordinary skill in the art at the time the invention was made.

In demonstrating utility, it has long been held that *in vitro* tests and tests using animal models can be sufficient to establish utility for therapeutic compositions and methods. (See, e.g., *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980)). In the present disclosure, Applicants report extensive testing of their MHC Class II constructs in an Experimental Autoimmune Encephalomyelitis (EAE) system, which system is a well-established and widely accepted model system for multiple sclerosis in humans. Using this conventional model system, Applicants have provided reliable and reproducible evidence that their MHC Class II constructs potently suppress the onset of EAE, and ameliorate the symptoms and progression of EAE. These data also clearly evince that the observed effects are mediated in an epitope-specific manner. (Specification, Example 5, page 50, line 27 to page 52, line 13). In related experiments, the specification clearly demonstrates that the claimed MHC Class II constructs and methods are effective for inhibiting epitope-specific T-cell proliferation and other T-cell immune responses (see, e.g., Example 4, page 49, line 26 to page 50, line 24; Example 12, page 79, line 15 to page 85, line 23). These experimental results are clearly sufficient to establish utility for the claimed invention.

The Office focuses on reported findings relating to myasthenia gravis patients, which studies have allegedly demonstrated that about 60% to 70% of antibodies against acetylcholine receptor (AChR) are directed against the “main immunogenic region” of AChR, which region may consist of more than one antigenic determinant. [Tzartos, S.J. et al., *J. Immunology* 134:2343-2349 (1985)] The Office asserts that “this leaves 30-40% of those endogenous anti-AChR to bind to undetermined immunoepitopes.” [Office Action, page 3].

This publication cited by the Office notably refers to autoantibodies, as opposed to antigen-specific T-cells. Applicants respectfully submit that on the basis of this fundamental and rather critical distinction, the subject reference is inapposite to the instantly-claimed invention.

Nonetheless, even if the epitope diversity and state of knowledge for T-cell epitopes were equitable with the findings of the Tzartos et al. report, it is clear from established authority that Applicants are not required to show that all potential T-cell epitopes are mapped and targeted by their RTL constructs, nor that all patients in a population can be effectively treated using the claimed compositions and methods. In the present case, one of ordinary skill in the art following the teachings of Applicant’s disclosure would readily understand that, for any particular antigen associated with a targeted autoimmune disease or condition, a certain percentage of patients may

be refractory to treatment for a variety of reasons. Nonetheless, it is reasonably expected based on Applicant's disclosure that a beneficial therapeutic response will often be elicited in patients presenting with a specific autoimmune disorder who are administered a "therapeutically effective amount of a purified MHC Class II polypeptide," (optionally including a multivalent panel of RTL constructs targeting multiple immunodominant epitopes involved in the targeted autoimmune disease). The prospect that some patients may be non-responsive to treatment according to the compositions and methods of the invention is not dispositive of utility. On the contrary, the disclosure is fully commensurate with the utility that artisans ordinarily would ordinarily expect for comparable therapeutic tools and methods.

The remaining comments presented by the Office to support the asserted utility rejection also fail to establish non-utility of Applicants' invention. In particular, the Office presents the following reasoning:

Treating a subject with a single epitope for treating an "epitope-specific immune response" therefore lacks utility because the treatment of that single response in a subject with an ongoing immune condition does not address epitope spreading and may exacerbate the subject's overall condition. (Office Action, page 3)

This alleged caveat to utility, relating to "epitope spreading", is specifically addressed in Applicants' disclosure by the contemplated use of a multivalent panel of MHC II peptide constructs targeting a plurality of antigenic determinants of autoimmune activity by T cells. The points in rebuttal presented above apply equally to this asserted ground for rejection. It is not sufficient to void the utility of Applicants' invention that the claimed compositions and methods may not be optimally effective, or that a certain percentage of patients may be refractory to treatment using the subject MHC Class II constructs.

There are numerous marketed drugs and biologics which are effective in some patients but not in all patients. For example, the overall response rate for HERCEPTIN®, a humanized monoclonal antibody approved for the treatment of metastatic breast cancer, when studied as a single agent in an open-label, multicenter, single-arm clinical trial in subjects with HER2 overexpressing metastatic breast cancer was 14%, with a 12% partial response rate and a 2% complete response rate. [See, Product Insert for HERCEPTIN®, page 1, column 2, a copy of which is attached hereto]

In view of the foregoing facts and authority, Applicants respectfully submit that one of ordinary skill in the art would readily discern the utility disclosed by Applicants for the claimed compositions and methods. Accordingly, withdrawal of the rejection of claims 37-40, 54 and 59-82 under 35 USC § 101 is earnestly solicited.

#### **Patentability Under 35 USC § 112, First Paragraph**

Claims 37-40, 54, and 59-82 are been rejected under 35 USC § 112 solely on the basis that, because the application allegedly fails to provide a credible or specific utility for the invention, it therefore allegedly fails to teach persons of ordinary skill in the art “how to use” the invention.

Applicants respectfully traverse this rejection for the reasons presented above. There are no substantive distinctions presented by the Office to support this “enablement” rejection beyond what was asserted in the context of utility, which is comprehensively addressed above.’

Applicants’ disclosure provides comprehensive description and guidance regarding how to construct, test, select, and administer active MHC II polypeptide constructs to effectively modulate T cell activity in mammalian subjects to elicit a therapeutically effective response. Notably, the

The Office has a burden of establishing sufficient factual evidence that is “inconsistent with” Applicants’ teachings and which establishes that the contested claims are not enabled. In re Marzocchi et al., 169 USPQ 367 (CCPA 1971). The arguments proffered the Office in the current record in no way contravenes Applicants’ clear and competent teachings summarized above and further evinced in the entire specification, incorporated herein.

In view of the foregoing facts and authority, Applicants respectfully submit that the rejection of claims 37-40, 54 and 59-82 under 35 USC § 112 is not adequately founded and should be withdrawn.

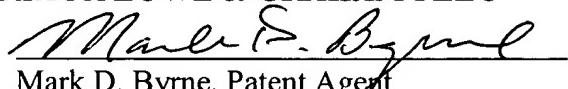
#### **CONCLUSION**

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance, and an official action to that end is urged. If the Examiner believes that a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at (206) 381-3300.

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Respectfully submitted,

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# Herceptin®

## Trastuzumab

### WARNINGS:

#### CARDIOMYOPATHY

HERCEPTIN administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with HERCEPTIN. Discontinuation of HERCEPTIN treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who received HERCEPTIN in combination with anthracyclines and cyclophosphamide. (See WARNINGS.)

#### HYPERSensitivity REACTIONS INCLUDING ANAPHYLAXIS

#### INFUSION REACTIONS

#### PULMONARY EVENTS

HERCEPTIN administration can result in severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary events. Rarely, these have been fatal. In most cases, symptoms occurred during or within 24 hours of administration of HERCEPTIN. HERCEPTIN infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of HERCEPTIN treatment should be strongly considered for patients who develop anaphylaxis, angioedema, or acute respiratory distress syndrome. (See WARNINGS.)

### DESCRIPTION

HERCEPTIN (Trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay ( $K_d = 5 \text{ nM}$ ) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2.<sup>12</sup> The antibody is an IgG, kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2.

The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary [CHO]) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

HERCEPTIN is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. The nominal content of each HERCEPTIN vial is 440 mg Trastuzumab, 400 mg  $\alpha$ ,  $\alpha$ -trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacterostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing 21 mg/mL Trastuzumab, at a pH of approximately 6.

### CLINICAL PHARMACOLOGY

#### General

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor.<sup>1</sup> HER2 protein overexpression is observed in 25%–30% of primary breast cancers. HER2 protein overexpression can be determined using immunohistochemistry (IHC) and gene amplification can be determined using fluorescence *in situ* hybridization (FISH) of fixed tumor blocks.<sup>2</sup> In referenced studies where HERCEPTIN use was not studied,<sup>3,4</sup> approximately 96%–98% of biopsy specimens that were found to have protein overexpression also had gene amplification and 100% of those with gene amplification also had protein overexpression.<sup>3,4</sup> The precision of the determination of protein overexpression or gene amplification, however, may vary depending on the sensitivity and specificity of the particular assay and assay procedures used (see PRECAUTIONS). When compared to the referenced studies noted above, the correlation between detectable protein overexpression using IHC and detectable gene amplification using FISH was not as high in the studies of HERCEPTIN clinical trial specimens (see CLINICAL STUDIES: HER2 Detection and HER2 Assay Concordance Studies, and PRECAUTIONS: HER2 Testing).

Trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.<sup>5</sup>

Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC).<sup>6,7</sup> *In vitro*, HERCEPTIN-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

#### Pharmacokinetics

The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively. Trastuzumab's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377  $\mu\text{g}/\text{mL}$ .

In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range=1 to 32 days) was observed. Between Weeks 16 and 32, Trastuzumab serum concentrations reached a steady state with mean trough and peak concentrations of approximately 79  $\mu\text{g}/\text{mL}$  and 123  $\mu\text{g}/\text{mL}$ , respectively.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the sera of some patients with HER2 overexpressing tumors. Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/mL (median=11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations. However, with weekly dosing, most patients with elevated shed antigen levels achieved target serum concentrations of Trastuzumab by Week 6.

Data suggest that the disposition of Trastuzumab is not altered based on age or serum creatinine (up to 2.0 mg/dL). No formal interaction studies have been performed.

Mean serum trough concentrations of Trastuzumab, when administered in combination with paclitaxel, were consistently elevated approximately 1.5-fold as compared with serum concentrations of Trastuzumab used in combination with anthracycline plus cyclophosphamide. In primate studies, administration of Trastuzumab with paclitaxel resulted in a reduction in Trastuzumab clearance. Serum levels of Trastuzumab in combination with cisplatin, doxorubicin or epirubicin plus cyclophosphamide did not suggest any interactions; no formal drug interaction studies were performed.

### CLINICAL STUDIES

The safety and efficacy of HERCEPTIN were studied in a randomized, controlled clinical trial in combination with chemotherapy (469 patients) and an open-label single agent clinical trial (222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the

### HERCEPTIN® [Trastuzumab]

HER2 protein. Patients were eligible if they had 2+ or 3+ levels of overexpression (based on a 0 to 3+ scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

A multicenter, randomized, controlled clinical trial was conducted in 469 patients with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease.<sup>1</sup> Patients were randomized to receive chemotherapy alone or in combination with HERCEPTIN given intravenously as a 4 mg/kg loading dose followed by weekly doses of HERCEPTIN at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m<sup>2</sup> over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m<sup>2</sup> or epirubicin 75 mg/m<sup>2</sup> plus 600 mg/m<sup>2</sup> cyclophosphamide every 21 days for six cycles). Compared with patients in the AC subgroups (n=281), patients in the paclitaxel subgroup (n=188) were more likely to have had the following: poor prognostic factors (premenopausal status, estrogen or progesterone receptor negative tumors, positive lymph nodes), prior therapy (adjuvant chemotherapy, myeloablative chemotherapy, radiotherapy), and a shorter disease-free interval. Sixty-five percent of patients randomized to receive chemotherapy alone in this study received HERCEPTIN at the time of disease progression as part of a separate extension study.

Compared with patients randomized to chemotherapy alone, the patients randomized to HERCEPTIN and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a longer median survival (see Table 1). These treatment effects were observed both in patients who received HERCEPTIN plus paclitaxel and in those who received HERCEPTIN plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup (see CLINICAL STUDIES: HER2 Detection).

**Table 1**  
Phase III Clinical Efficacy in First-Line Treatment

|                                      | Combined Results  |                                       | Paclitaxel Subgroup                      |  | AC Subgroup                        |                                   |
|--------------------------------------|---|---------------------------------------|--|--|------------------------------------|-----------------------------------|
|                                      | HERCEPTIN<br>+<br>All<br>Chemo-<br>therapy<br>(n = 235) | All<br>Chemo-<br>therapy<br>(n = 234) | HERCEPTIN<br>+<br>Paclitaxel<br>(n = 92) | HERCEPTIN<br>+<br>Paclitaxel<br>(n = 96) | HERCEPTIN<br>+<br>AC*<br>(n = 143) | HERCEPTIN<br>+<br>AC<br>(n = 138) |
| <b>Primary Endpoint</b>              |   |                                       |  |  |                                    |                                   |
| Time to Progression <sup>a,b,c</sup> |   |                                       |  |  |                                    |                                   |
| Median (months)                      | 7.2   | 4.5                                   | 6.7                                      | 2.5                                      | 7.6                                | 5.7                               |
| 95% confidence interval              | 6.9, 8.2  | 4.3, 4.9                              | 5.2, 9.9                                 | 2.0, 4.3                                 | 7.2, 9.1                           | 4.6, 7.1                          |
| p-value (log rank)                   | <0.0001   |                                       | <0.0001                                  |  | 0.002                              |                                   |
| <b>Secondary Endpoints</b>           |   |                                       |  |  |                                    |                                   |
| Overall Response Rate <sup>b</sup>   |   |                                       |  |  |                                    |                                   |
| Rate (percent)                       | 45  | 29                                    | 38                                       | 15                                       | 50                                 | 38                                |
| 95% confidence interval              | 39, 51  | 23, 35                                | 28, 48                                   | 8, 22                                    | 42, 58                             | 30, 46                            |
| p-value ( $\chi^2$ -test)            | <.0001  |                                       | <.0001                                   |  | 0.10                               |                                   |
| Duration of Response <sup>b,c</sup>  |   |                                       |  |  |                                    |                                   |
| Median (months)                      | 8.3   | 5.8                                   | 8.3                                      | 4.3                                      | 8.4                                | 6.4                               |
| 25%, 75% quartile                    | 5.5, 14.8   | 3.9, 8.5                              | 5.1, 11.0                                | 3.7, 7.4                                 | 5.8, 14.8                          | 4.5, 8.5                          |
| Survival Time <sup>c</sup>           |   |                                       |  |  |                                    |                                   |
| Median Survival (months)             | 25.1  | 20.3                                  | 22.1                                     | 18.4                                     | 26.8                               | 21.4                              |
| 95% confidence interval              | 22.2, 29.5  | 16.8, 24.2                            | 16.9, 28.6                               | 12.7, 24.4                               | 23.3, 32.9                         | 18.3, 26.6                        |
| p-value (log rank)                   | 0.05  |                                       | 0.17                                     |  | 0.16                               |                                   |

\*AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

<sup>a</sup>Assessed by an independent Response Evaluation Committee.

<sup>b</sup>Kaplan-Meier Estimate.

HERCEPTIN was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of HERCEPTIN at 2 mg/kg IV. The ORR (complete response + partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate. Complete responses were observed only in patients with disease limited to skin and lymph nodes (see CLINICAL STUDIES: HER2 Detection).

#### HER2 Detection

(See PRECAUTIONS: HER2 Testing)

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for HERCEPTIN therapy (see INDICATIONS AND USAGE). Overexpression of HER2 by tumors was an entry criterion of the two clinical studies described above. In those studies, a research-use-only IHC assay (referred to as the Clinical Trial Assay [CTA]) was used.

The commercial assays described below, HercepTest® (IHC assay) and PathVysion® (FISH assay), are appropriate assays to aid in the selection of patients for HERCEPTIN therapy (see HER2 Protein Overexpression Detection Methods and HER2 Gene Amplification Detection Methods). The comparability of either assay with regard to the ability to predict clinical benefit from HERCEPTIN therapy has not been prospectively studied. In addition, the utility of either assay in patients whose tumors would score as 0 or 1+ by the CTA has not been established because patients with tumors that scored as 0 or 1+ were excluded from the clinical studies described.

#### HER2 Protein Overexpression Detection Methods

HER2 protein overexpression can be established by measuring expressed HER2 protein using IHC methodology. In the clinical trials described above, specimens were tested with the CTA and scored as 0, 1+, 2+, or 3+ with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Data from the randomized trial suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 2). In an exploratory analysis, the relative risk (rr) for time to progression was lower in the patients whose tumors tested as CTA 3+ (rr = 0.42 with 95% CI: 0.33, 0.54) than in those tested as CTA 2+ (rr = 0.76 with 95% CI: 0.50, 1.15). The relative risk represents the risk of progression in the HERCEPTIN plus chemotherapy arm versus the chemotherapy arm. Therefore, a lower ratio represents longer time to progression in the HERCEPTIN arm. In the single-arm study of HERCEPTIN as a single agent, the overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that tested as CTA 2+, it was 6%.

HercepTest®, another IHC assay, was assessed for concordance with the CTA (see HER2 Assay Concordance Studies), but has not been used to assess tumor specimens from the HERCEPTIN clinical studies described above.

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### HER2 Gene Amplification Detection Methods

As a surrogate for protein overexpression, measurement of the number of HER2 gene copies using FISH to detect gene amplification may be employed. An exploratory, retrospective assessment of known CTA 2+ or 3+ tumor specimens was performed to detect HER2 gene amplification using PathVision®, a FISH assay. Data from this retrospective analysis involving 660 of 691 (96%) patients enrolled in the clinical studies (all scoring 2+ or 3+ by the CTA) suggested that the beneficial treatment effects were greater in patients whose tumors tested as FISH (+) than in those that were FISH (-); however, time to progression was prolonged for patients on the HERCEPTIN arm, regardless of the FISH result (see Table 2). In the single arm study of HERCEPTIN as a single agent, the overall response rate in patients whose tumors tested as FISH (+) was 20%, while in those tested as FISH (-), there were no responses.

These data are not sufficient to conclude whether FISH testing can distinguish a subpopulation of CTA 2+ patients who would be unlikely to benefit from HERCEPTIN therapy. In addition, there are no data correlating clinical outcome with FISH test results for patients with tumors that scored as 0 or 1+ by CTA; therefore, conclusions regarding the usefulness of FISH in the general population cannot be made.

**Table 2**  
Treatment Effect versus Level of HER2 Expression  
Phase III Randomized Trial (N = 469):  
HERCEPTIN Plus Chemotherapy versus Chemotherapy

| HER2 Assay Result | Number of Patients (N) | Relative Risk** for Time to Disease Progression (95% CI) | Relative Risk** for Mortality (95% CI) |
|-------------------|------------------------|--|--|
| CTA 2+ or 3+      | 469                    | 0.49 (0.40, 0.61)  | 0.80 (0.64, 1.00)                      |
|                   | 325                    | 0.44 (0.34, 0.57)  | 0.70 (0.53, 0.91)                      |
|                   | 126                    | 0.62 (0.42, 0.94)  | 1.06 (0.70, 1.63)                      |
| CTA 2+            | 120                    | 0.76 (0.50, 1.15)  | 1.26 (0.82, 1.94)                      |
|                   | 32                     | 0.54 (0.21, 1.35)  | 1.31 (0.53, 3.27)                      |
|                   | 83                     | 0.77 (0.48, 1.25)  | 1.11 (0.68, 1.82)                      |
| CTA 3+            | 349                    | 0.42 (0.33, 0.54)  | 0.70 (0.51, 0.90)                      |
|                   | 293                    | 0.42 (0.32, 0.55)  | 0.67 (0.51, 0.89)                      |
|                   | 43                     | 0.43 (0.20, 0.94)  | 0.88 (0.39, 1.98)                      |

\*FISH testing results were available for 451 of the 469 patients enrolled on study.

\*\*The relative risk represents the risk of progression or death in the HERCEPTIN plus chemotherapy arm versus the chemotherapy arm.

### HER2 Assay Concordance Studies

(See PRECAUTIONS: HER2 Testing)

**Immunohistochemistry:** The DAKO HercepTest®, an IHC test for detecting HER2 protein overexpression, has not been directly studied for its ability to predict HERCEPTIN treatment effect, but has been compared to the CTA on over 500 breast cancer histology specimens obtained from the National Cancer Institute Cooperative Breast Cancer Tissue Resource. Based upon these results, of specimens testing 3+ (strongly positive) on the HercepTest®, 82% were 3+ (i.e., the reading most associated with clinical benefit), 12% were 2+, and 6% were 0 or 1+ on the CTA. The 6% of HercepTest® 3+ specimens that were CTA 0 or 1+ would be expected to represent 2% of the 0 and 1+ population. Of specimens testing 2+ (weakly positive) on the HercepTest®, 14% were 3+, 20% were 2+, and 66% were 0 or 1+ on the CTA. Of specimens testing 0 or 1+ on the HercepTest®, 2% were 3+, 6% were 2+, and 92% were 0 or 1+ on the CTA.

**Fluorescence In Situ Hybridization:** The Vysis PathVision® HER2 DNA Probe, a FISH test for detecting HER2 gene amplification, was compared with the CTA on over 500 breast cancer histology specimens originally submitted for potential enrollment in the HERCEPTIN trials. A HER2:CEP17 ratio of ≥2 was defined as FISH positive (+). Based on these results, of specimens testing FISH (+) by PathVision®, 81% were 3+, 10% were 2+, and 9% were 0 or 1+ on the CTA. The 9% of FISH (+) specimens that were CTA 0 or 1+ would be expected to represent 3% of the total CTA 0 or 1+ population. Of specimens testing FISH (-) by PathVision®, 3% were 3+, 10% were 2+, and 87% were 0 or 1+ on the CTA.

### INDICATIONS AND USAGE

HERCEPTIN (Trastuzumab) as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. HERCEPTIN in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. HERCEPTIN should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression (see PRECAUTIONS: HER2 Testing and CLINICAL STUDIES: HER2 Detection).

### CONTRAINDICATIONS

None known.

### WARNINGS

#### Cardiotoxicity

Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S<sub>3</sub> gallop, or reduced ejection fraction, have been observed in patients treated with HERCEPTIN. Congestive heart failure associated with HERCEPTIN therapy may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke (see BOXED WARNINGS: CARDIOMYOPATHY). The clinical status of patients in the trials who developed congestive heart failure was classified for severity using the New York Heart Association classification system (I-IV, where IV is the most severe level of cardiac failure) (see Table 3).

**Table 3**  
Incidence and Severity of Cardiac Dysfunction

|                         | HERCEPTIN® Alone<br>n=213 | HERCEPTIN® + Paclitaxel®<br>n=91 | Paclitaxel®<br>n=95 | HERCEPTIN® + Anthracycline<br>+ Cyclophosphamide®<br>n=143 | Anthracycline +<br>Cyclophosphamide®<br>n=135 |
|-------------------------|---------------------------|----------------------------------|---------------------|--|---|
| Any Cardiac Dysfunction | 7%                        | 11%                              | 1%                  | 28%  | 7%  |
| Class III-IV            | 5%                        | 4%                               | 1%                  | 19%  | 3%  |

\*Open-label, single-agent Phase II study (94% received prior anthracyclines).

\*Randomized Phase III study comparing chemotherapy plus HERCEPTIN to chemotherapy alone, where chemotherapy is either anthracycline/cyclophosphamide or paclitaxel.

Candidates for treatment with HERCEPTIN should undergo thorough baseline cardiac assessment including history and physical exam and one or more of the following: EKG, echocardiogram, and MUGA scan. There are no data regarding the most appropriate method of evaluation for the identification of patients at risk for developing cardiotoxicity. Monitoring may not identify all patients who will develop cardiac dysfunction.

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**Extreme caution** should be exercised in treating patients with pre-existing cardiac dysfunction.

Patients receiving HERCEPTIN should undergo frequent monitoring for deteriorating cardiac function.

The probability of cardiac dysfunction was highest in patients who received HERCEPTIN concurrently with anthracyclines. The data suggest that advanced age may increase the probability of cardiac dysfunction.

Pre-existing cardiac disease or prior cardiotoxic therapy (e.g., anthracycline or radiation therapy to the chest) may decrease the ability to tolerate HERCEPTIN therapy; however, the data are not adequate to evaluate the correlation between HERCEPTIN-induced cardiotoxicity and these factors.

Discontinuation of HERCEPTIN therapy should be strongly considered in patients who develop clinically significant congestive heart failure. In the clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy often including discontinuation of HERCEPTIN. The safety of continuation or resumption of HERCEPTIN in patients who have previously experienced cardiac toxicity has not been studied. There are insufficient data regarding discontinuation of HERCEPTIN therapy in patients with asymptomatic decreases in ejection fraction; such patients should be closely monitored for evidence of clinical deterioration.

### Hypersensitivity Reactions Including Anaphylaxis

Severe hypersensitivity reactions have been infrequently reported in patients treated with HERCEPTIN (see BOXED WARNINGS: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS). Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. The onset of symptoms generally occurred during an infusion, but there have also been reports of symptom onset after the completion of an infusion. Reactions were most commonly reported in association with the initial infusion.

HERCEPTIN infusion should be interrupted in all patients with severe hypersensitivity reactions. In the event of a hypersensitivity reaction, appropriate medical therapy should be administered, which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with HERCEPTIN after experiencing a severe hypersensitivity reaction. HERCEPTIN has been readministered to some patients who fully recovered from a previous severe reaction. Prior to readministration of HERCEPTIN, the majority of these patients were prophylactically treated with pre-medications including antihistamines and/or corticosteroids. While some of these patients tolerated retreatment, others had severe reactions again despite the use of prophylactic pre-medications.

### Infusion Reactions

In the postmarketing setting, rare occurrences of severe infusion reactions leading to a fatal outcome have been associated with the use of HERCEPTIN (see BOXED WARNINGS: INFUSION REACTIONS).

In clinical trials, infusion reactions consisted of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. These reactions were usually mild to moderate in severity (see ADVERSE REACTIONS).

However, in postmarketing reports, more severe adverse reactions to HERCEPTIN infusion were observed and included bronchospasm, hypoxia, and severe hypotension. These severe reactions were usually associated with the initial infusion of HERCEPTIN and generally occurred during or immediately following the infusion. However, the onset and clinical course were variable. For some patients, symptoms progressively worsened and led to further pulmonary complications (see WARNINGS: Pulmonary Events). In other patients with acute onset of signs and symptoms, initial improvement was followed by clinical deterioration. Delayed post-infusion events with rapid clinical deterioration have also been reported. Rarely, severe infusion reactions culminated in death within hours or up to one week following an infusion.

Some severe reactions have been treated successfully with interruption of the HERCEPTIN infusion and supportive therapy including oxygen, intravenous fluids, beta-agonists, and corticosteroids.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with HERCEPTIN after experiencing a severe infusion reaction. HERCEPTIN has been readministered to some patients who fully recovered from the previous severe reaction. Prior to readministration of HERCEPTIN, the majority of these patients were prophylactically treated with pre-medications including antihistamines and/or corticosteroids. While some of these patients tolerated retreatment, others had severe reactions again despite the use of prophylactic pre-medications.

### Exacerbation of Chemotherapy-Induced Neutropenia

In randomized, controlled clinical trials designed to assess the impact of the addition of HERCEPTIN on chemotherapy, the per-patient incidences of moderate to severe neutropenia and of febrile neutropenia were higher in patients receiving HERCEPTIN in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. In the postmarketing setting, deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving HERCEPTIN and myelosuppressive chemotherapy, although in controlled clinical trials (pre- and post-marketing), the incidence of septic deaths was not significantly increased. The pathophysiologic basis for exacerbation of neutropenia has not been determined; the effect of HERCEPTIN on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated (see ADVERSE REACTIONS: Anemia and Leukopenia; ADVERSE REACTIONS: Infection).

### Pulmonary Events

Severe pulmonary events leading to death have been reported rarely with the use of HERCEPTIN in the postmarketing setting. Signs, symptoms and clinical findings include dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, and acute respiratory distress syndrome. These events may or may not occur as sequelae of infusion reactions (see WARNINGS: Infusion Reactions). Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk of severe reactions.

Other severe events reported rarely in the postmarketing setting include pneumonitis and pulmonary fibrosis.

### PRECAUTIONS

#### General

HERCEPTIN therapy should be used with caution in patients with known hypersensitivity to Trastuzumab, Chinese Hamster Ovary cell proteins, or any component of this product.

#### HER2 Testing

Assessment for HER2 overexpression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the HercepTest® and PathVision® package inserts for full instructions on assay performance (see CLINICAL STUDIES: HER2 Detection).

#### Drug Interactions

There have been no formal drug interaction studies performed with HERCEPTIN in humans. Administration of paclitaxel in combination with HERCEPTIN resulted in a two-fold decrease in HERCEPTIN clearance in a non-human primate study and in a 1.5-fold increase in HERCEPTIN serum levels in clinical studies (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

## HERCEPTIN® (Trastuzumab)

### Benzyl Alcohol

For patients with a known hypersensitivity to benzyl alcohol (the preservative in Bacteriostatic Water for Injection) reconstitute HERCEPTIN with Sterile Water for Injection (SWFI), USP. DISCARD THE SWFI-RECONSTITUTED HERCEPTIN VIAL FOLLOWING A SINGLE USE.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

HERCEPTIN has not been tested for its carcinogenic potential.

#### Mutagenesis

No evidence of mutagenic activity was observed in Ames tests using six different test strains of bacteria, with and without metabolic activation, at concentrations of up to 5000 µg/mL Trastuzumab. Human peripheral blood lymphocytes treated *in vitro* at concentrations of up to 5000 µg/plate Trastuzumab, with and without metabolic activation, revealed no evidence of mutagenic potential. In an *in vivo* mutagenic assay (the micronucleus assay), no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg Trastuzumab.

#### Impairment of Fertility

A fertility study has been conducted in female cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg HERCEPTIN and has revealed no evidence of impaired fertility.

### Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, HERCEPTIN should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In the postmarketing setting, oligohydramnios has been reported in women who received HERCEPTIN during pregnancy, either in combination with chemotherapy or as a single agent. Given the limited number of reported cases, the high background rate of occurrence of oligohydramnios, the lack of clear temporal relationships between drug use and clinical findings, and the lack of supportive findings in animal studies, an association between HERCEPTIN and oligohydramnios has not been established.

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg HERCEPTIN and have revealed no evidence of impaired fertility or harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation.<sup>12</sup> Placental transfer of HERCEPTIN during the early (Days 20–50 of gestation) and late (Days 120–150 of gestation) fetal development period was observed in monkeys.

### Nursing Mothers

A study conducted in lactating cynomolgus monkeys at doses 25 times the weekly human maintenance dose of 2 mg/kg HERCEPTIN demonstrated that Trastuzumab is secreted in the milk. The presence of Trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 3 months of age. It is not known whether HERCEPTIN is secreted in human milk. Because human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during HERCEPTIN therapy and for 6 months after the last dose of HERCEPTIN.

### Pediatric Use

The safety and effectiveness of HERCEPTIN in pediatric patients have not been established.

### Geriatric Use

HERCEPTIN has been administered to 133 patients who were 65 years of age or over. The risk of cardiac dysfunction may be increased in geriatric patients. The reported clinical experience is not adequate to determine whether older patients respond differently from younger patients.

### ADVERSE REACTIONS

The most serious adverse reactions caused by HERCEPTIN include cardiomyopathy, hypersensitivity reactions including anaphylaxis, infusion reactions, pulmonary events, and exacerbation of chemotherapy-induced neutropenia. Please refer to the BOXED WARNINGS and/or WARNINGS sections for detailed descriptions of these reactions. The most common adverse reactions associated with HERCEPTIN use are fever, diarrhea, infections, chills, increased cough, headache, rash, and insomnia.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Additional adverse reactions have been identified during post-marketing use of HERCEPTIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HERCEPTIN exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to HERCEPTIN.

Where specific percentages are noted, these data are based on clinical studies of HERCEPTIN alone or in combination with chemotherapy in clinical trials. Data in Table 4 are based on the experience with the recommended dosing regimen for HERCEPTIN in a randomized controlled clinical trial of 234 patients who received HERCEPTIN in combination with chemotherapy and four open-label studies of HERCEPTIN as a single agent in 352 patients at doses of 10–500 mg administered weekly. Data regarding serious adverse events are based on experience in 958 patients enrolled in all clinical trials of HERCEPTIN conducted prior to marketing approval.

### Cardiac Failure/Dysfunction

For a description of cardiac toxicities, see BOXED WARNINGS: CARDIOMYOPATHY and WARNINGS: Cardiotoxicity.

### Anemia and Leukopenia

In a randomized, controlled trial (see CLINICAL STUDIES), the per-patient incidences of anemia (30% vs. 21%) and leukopenia (53% vs. 37%) were higher in patients receiving HERCEPTIN in combination with chemotherapy as compared to those receiving chemotherapy alone. The majority of these cytopenic events were mild to moderate in intensity, reversible, and none resulted in discontinuation of therapy with HERCEPTIN.

In a randomized, controlled trial conducted in the post-marketing setting, there were also increased incidences of NCI-CTC Grade 3/4 neutropenia (32% [29/92] vs. 22% [21/94]) and of febrile neutropenia (23% [21/91] vs. 17% [16/94]) in patients randomized to HERCEPTIN in combination with myelosuppressive chemotherapy as compared to chemotherapy alone (see ADVERSE REACTIONS: Infection).

Hematologic toxicity is infrequent following the administration of HERCEPTIN as a single agent, with an incidence of Grade III toxicities for WBC, platelets, hemoglobin all <1%. No Grade IV toxicities were observed.

### Diarrhea

Of patients treated with HERCEPTIN as a single agent, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in patients receiving HERCEPTIN in combination with chemotherapy.

### Infection

In a randomized, controlled trial (see CLINICAL STUDIES), the incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, was higher

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(46% vs. 30%) in patients receiving HERCEPTIN in combination with chemotherapy as compared to those receiving chemotherapy alone.

In a randomized, controlled trial conducted in the post-marketing setting, the reported incidence of febrile neutropenia was higher (23% [21/92] vs. 17% [16/94]) in patients receiving HERCEPTIN in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

In the postmarketing setting, there have also been reports of febrile neutropenia and infection with neutropenia culminating in death associated with the use of HERCEPTIN and myelosuppressive chemotherapy (see WARNINGS: Exacerbation of Chemotherapy-Induced Neutropenia).

### Infusion Reactions

During the first infusion with HERCEPTIN, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients in clinical trials. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of HERCEPTIN infusion). HERCEPTIN discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. The symptoms occurred infrequently with subsequent HERCEPTIN infusions (see BOXED WARNINGS: INFUSION REACTIONS and WARNINGS: Infusion Reactions).

### Hypersensitivity Reactions Including Anaphylaxis

#### Pulmonary Events

In the postmarketing setting, severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary adverse events have been reported (see BOXED WARNINGS: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS and WARNINGS: Hypersensitivity Reactions Including Anaphylaxis). These events include anaphylaxis, angioedema, bronchospasm, hypotension, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see WARNINGS.

### Glomerulopathy

In the postmarketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiation of HERCEPTIN therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure.

**Table 4**  
Adverse Events Occurring in ≥5% of Patients or at Increased Incidence in the HERCEPTIN Arm of the Randomized Study  
(Percent of Patients)

|                             | Single Agent n=352 | HERCEPTIN + Paclitaxel n=91 | Paclitaxel Alone n=95 | HERCEPTIN + AC n=143 | AC Alone n=135 |
|-----------------------------|--------------------|-----------------------------|-----------------------|----------------------|----------------|
| <b>Body as a Whole</b>      |                    |                             |                       |                      |                |
| Pain                        | 47                 | 61                          | 62                    | 57                   | 42             |
| Asthenia                    | 42                 | 62                          | 57                    | 54                   | 55             |
| Fever                       | 35                 | 49                          | 23                    | 56                   | 34             |
| Chills                      | 32                 | 41                          | 4                     | 35                   | 11             |
| Headache                    | 26                 | 36                          | 28                    | 44                   | 31             |
| Abdominal pain              | 22                 | 34                          | 22                    | 23                   | 18             |
| Back pain                   | 22                 | 34                          | 30                    | 27                   | 15             |
| Infection                   | 20                 | 47                          | 27                    | 47                   | 31             |
| Flu syndrome                | 10                 | 12                          | 5                     | 12                   | 6              |
| Accidental injury           | 6                  | 13                          | 3                     | 9                    | 4              |
| Allergic reaction           | 3                  | 8                           | 2                     | 4                    | 2              |
| <b>Cardiovascular</b>       |                    |                             |                       |                      |                |
| Tachycardia                 | 5                  | 12                          | 4                     | 10                   | 5              |
| Congestive heart failure    | 7                  | 11                          | 1                     | 28                   | 7              |
| <b>Digestive</b>            |                    |                             |                       |                      |                |
| Nausea                      | 33                 | 51                          | 9                     | 76                   | 77             |
| Diarrhea                    | 25                 | 45                          | 29                    | 45                   | 26             |
| Vomiting                    | 23                 | 37                          | 28                    | 53                   | 49             |
| Nausea and vomiting         | 8                  | 14                          | 11                    | 18                   | 9              |
| Anorexia                    | 14                 | 24                          | 16                    | 31                   | 26             |
| <b>Heme &amp; Lymphatic</b> |                    |                             |                       |                      |                |
| Anemia                      | 4                  | 14                          | 9                     | 36                   | 26             |
| Leukopenia                  | 3                  | 24                          | 17                    | 52                   | 34             |
| <b>Metabolic</b>            |                    |                             |                       |                      |                |
| Peripheral edema            | 10                 | 22                          | 20                    | 20                   | 17             |
| Edema                       | 8                  | 10                          | 8                     | 11                   | 5              |
| <b>Musculoskeletal</b>      |                    |                             |                       |                      |                |
| Bone pain                   | 7                  | 24                          | 18                    | 7                    | 7              |
| Arthralgia                  | 6                  | 37                          | 21                    | 8                    | 9              |
| <b>Nervous</b>              |                    |                             |                       |                      |                |
| Insomnia                    | 14                 | 25                          | 13                    | 29                   | 15             |
| Dizziness                   | 13                 | 22                          | 24                    | 24                   | 18             |
| Paresthesia                 | 9                  | 48                          | 39                    | 17                   | 11             |
| Depression                  | 6                  | 12                          | 13                    | 20                   | 12             |
| Peripheral neuritis         | 2                  | 23                          | 16                    | 2                    | 2              |
| Neuropathy                  | 1                  | 13                          | 5                     | 4                    | 4              |
| <b>Respiratory</b>          |                    |                             |                       |                      |                |
| Cough increased             | 26                 | 41                          | 22                    | 43                   | 29             |
| Dyspnea                     | 22                 | 27                          | 26                    | 42                   | 25             |
| Rhinitis                    | 14                 | 22                          | 5                     | 22                   | 16             |
| Pharyngitis                 | 12                 | 22                          | 14                    | 30                   | 18             |
| Sinusitis                   | 9                  | 21                          | 7                     | 13                   | 6              |
| <b>Skin</b>                 |                    |                             |                       |                      |                |
| Rash                        | 18                 | 38                          | 18                    | 27                   | 17             |
| Herpes simplex              | 2                  | 12                          | 3                     | 7                    | 9              |
| Acne                        | 2                  | 11                          | 3                     | 3                    | <1             |
| <b>Urogenital</b>           |                    |                             |                       |                      |                |
| Urinary tract infection     | 5                  | 18                          | 14                    | 13                   | 7              |

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### **Other Serious Adverse Events**

The following other serious adverse events occurred in at least one of the 958 patients treated with HERCEPTIN in clinical studies:

**Body as a Whole:** cellulitis, anaphylactoid reaction, ascites, hydrocephalus, radiation injury, deafness, amblyopia

**Cardiovascular:** vascular thrombosis, pericardial effusion, heart arrest, hypotension, syncope, hemorrhage, shock, arrhythmia

**Digestive:** hepatic failure, gastroenteritis, hematemesis, ileus, intestinal obstruction, colitis, esophageal ulcer, stomatitis, pancreatitis, hepatitis

**Endocrine:** hypothyroidism

**Hematological:** pancytopenia, acute leukemia, coagulation disorder, lymphangitis

**Metabolic:** hypercalcemia, hypomagnesemia, hyponatremia, hypoglycemia, growth retardation, weight loss

**Musculoskeletal:** pathological fractures, bone necrosis, myopathy

**Nervous:** convulsion, ataxia, confusion, manic reaction

**Respiratory:** apnea, pneumothorax, asthma, hypoxia, laryngitis

**Skin:** herpes zoster, skin ulceration

**Urinary:** hydronephrosis, kidney failure, cervical cancer, hematuria, hemorrhagic cystitis, pyelonephritis

### **Immunogenicity**

Of 903 patients who have been evaluated, human anti-human antibody (HAHA) to Trastuzumab was detected in one patient, who had no allergic manifestations.

The data reflect the percentage of patients whose test results were considered positive for antibodies to HERCEPTIN in the HAHA assay for Trastuzumab, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to HERCEPTIN with the incidence of antibodies to other products may be misleading.

### **OVERDOSAGE**

There is no experience with overdosage in human clinical trials. Single doses higher than 500 mg have not been tested.

### **DOSAGE AND ADMINISTRATION**

#### **Usual Dose**

The recommended initial loading dose is 4 mg/kg Trastuzumab administered as a 90-minute infusion. The recommended weekly maintenance dose is 2 mg/kg Trastuzumab and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. HERCEPTIN may be administered in an outpatient setting. HERCEPTIN is to be diluted in saline for IV infusion. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** (See DOSAGE AND ADMINISTRATION: Administration.)

#### **Preparation for Administration**

The diluent provided has been formulated to maintain the stability and sterility of HERCEPTIN for up to 28 days. Other diluents have not been shown to contain effective preservatives for HERCEPTIN. Each vial of HERCEPTIN should be reconstituted with 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied, to yield a multi-dose solution containing 21 mg/mL Trastuzumab. Immediately upon reconstitution with BWFI, the vial of HERCEPTIN must be labeled in the area marked "Do not use after:" with the future date that is 28 days from the date of reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, HERCEPTIN must be reconstituted with Sterile Water for Injection (see PRECAUTIONS). HERCEPTIN WHICH HAS BEEN RECONSTITUTED WITH SWFI MUST BE USED IMMEDIATELY AND ANY UNUSED PORTION DISCARDED. USE OF OTHER RECONSTITUTION DILUENTS SHOULD BE AVOIDED.

Shaking the reconstituted HERCEPTIN or causing excessive foaming during the addition of diluent may result in problems with dissolution and the amount of HERCEPTIN that can be withdrawn from the vial.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Trastuzumab. The stream of diluent should be directed into the lyophilized cake.
- Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. **DO NOT SHAKE.**
- Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The solution should be essentially free of visible particulates, clear to slightly opalescent and colorless to pale yellow.

Determine the number of mg of Trastuzumab needed, based on a loading dose of 4 mg Trastuzumab/kg body weight or a maintenance dose of 2 mg Trastuzumab/kg body weight. Calculate the volume of 21 mg/mL Trastuzumab solution and withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DEXTOSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

No incompatibilities between HERCEPTIN and polyvinylchloride or polyethylene bags have been observed.

#### **Administration**

Treatment may be administered in an outpatient setting by administration of a 4 mg/kg Trastuzumab loading dose by intravenous (IV) infusion over 90 minutes. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** Patients should be observed for fever and chills or other infusion-associated symptoms (see BOXED WARNINGS, WARNINGS, and ADVERSE REACTIONS). If prior infusions are well tolerated, subsequent weekly doses of 2 mg/kg Trastuzumab may be administered over 30 minutes.

**HERCEPTIN should not be mixed or diluted with other drugs. HERCEPTIN infusions should not be administered or mixed with dextrose solutions.**

#### **Stability and Storage**

Vials of HERCEPTIN are stable at 2–8°C (36–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of HERCEPTIN reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2–8°C (36–46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted HERCEPTIN solution should be used immediately and any unused portion must be discarded. **DO NOT FREEZE HERCEPTIN THAT HAS BEEN RECONSTITUTED.**

The solution of HERCEPTIN for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, may be stored at 2–8°C (36–46°F) for up to 24 hours prior to use. Diluted HERCEPTIN has been shown to be stable for up to 24 hours at room temperature (2–25°C). However, because diluted HERCEPTIN contains no effective preservative, the reconstituted and diluted solution should be stored refrigerated (2–8°C).

## **HERCEPTIN® [Trastuzumab]**

### **HOW SUPPLIED**

HERCEPTIN (Trastuzumab) is supplied as a lyophilized, sterile powder nominally containing 440 mg Trastuzumab per vial under vacuum.

Each carton contains one vial of 440 mg HERCEPTIN® (Trastuzumab) and one vial containing 20 mL of Bacteriostatic Water for Injection, USP, 1.1% benzyl alcohol. NDC 50242-134-68.

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### **HERCEPTIN®**

#### **[Trastuzumab]**

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